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EXAMINER

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/937,103
Filing Date: July 05, 2002
Appellant(s): GRAF ET AL.

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GROUP 1600

GRAF ET AL.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 1, 2006 appealing the Office action mailed August 30, 2005.

This action is a Supplement Examiner's Answer. This action is submitted to correct improper headings. The appeal brief was filed August 1, 2006 appealing from the Office action mailed.

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct.

(4) *Status of Amendments After Final*

Appellant's statement that an amendment filed February 24, 2006 which cancelled claims 2-8, 11-15 and 17 directed to compositions of matter is correct.

(5) *Summary of Claimed Subject Matter*

The summary of invention contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the issues in the brief is correct.

(7) Claims Appendix

Appellant's copy of the appealed claims contained in the appendix is correct.

(8) Evidence Relied Upon

Samaritani (*WO 96/29095 published September 26, 1996*).

Sola-Penna et al (*Archives of Biochemistry and Biophysics, Vol. 360, No. 1, December 1, 1998, p. 10-14*)

Anderson et al (*U.S. Patent No. 5,097,020 published March 17, 1992*).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 9-10 and 16 are rejected under U.S.C. 103(a) as unpatentable over Samaritani (*WO 96/29095 published September 26, 1996*) in view of Sola-Penna et al (*Archives of Biochemistry and Biophysics, Vol. 360., No. 1, December 1, 1998, p. 10-14*) and further in view of Anderson et al (*U.S. Patent No. 5, 097, 020 published March 17, 1992*).

Samaritani teaches a method of preserving the immunogenicity of a pharmaceutical composition maintained in liquid form over time by using non-reducing sugars to stabilize these compositions (see the Abstract and page 1).

Samaritani does not teach the non-reducing sugar trehalose.

Sola-Penna et al teach that trehalose is more effective at stabilizing compositions than other sugars (see the Abstract and the Title). Sola-Penna et al teach that trehalose is the best stabilizer of macromolecules because trehalose has the ability to protect these molecules from thermal inactivation (see the Abstract). Sola-Penna et al teach compositions comprising trehalose wherein the quantity of trehalose is about 5% by mass.

Samaritani nor Sola-Penna et al teach vaccine compositions comprising an antigen consisting of a polysaccharide bound to a carrier protein.

Anderson et al teach a vaccine comprising covalent attachment of capsular polymer fragment derived from bacterial capsular polymers to bacterial toxoids (column 2, lines 58-64). Anderson et al teach that suitable carrier proteins of the inventions include diphtheria and tetanus toxoids (columns 5, lines 29-36). Anderson et al teach that vaccines of the invention include vaccines against systemic infections caused by the pathogens *Haemophilus influenzae* type b, *E. coli*, pneumococcus, meningococcus, streptococcus and pseudomonas (column 6, lines 59-65). Anderson et al teach that the regulation of any reaction parameter, e.g. time, temperature, pH, etc. which affects the reactivity or rate of reaction will alter the final composition and structure of the conjugate (column 4, lines 45-49). Anderson et al teach that the vaccines of the invention have been lyophilized (column 18, lines 35-40). Anderson et al teach that the conjugates of the invention appear to convert into macromolecular aggregates after preparation (column 13, lines 67-68 and column 14, lines 1-2).

It would have been *prima facie* obvious at the time the invention was made to use trehalose to stabilize a liquid vaccine composition comprising an antigen (polysaccharide bound to a carrier molecule) used in a method to preserve the immunogenicity of the vaccine composition over time because Samaritani teaches that non-reducing sugars can be used to stabilize pharmaceutical compositions that are maintained in the liquid state and Sola-Penna et al teach that trehalose is the best stabilizer of macromolecules. It would be expected barring evidence to the contrary that trehalose would be effective in stabilizing pharmaceutical compositions that are maintained in the liquid state because Samaritani teaches that non-reducing sugars can stabilize compositions in the liquid state to avoid processes such as lyophilization thereby making the compositions readily injectable.

(10) Response to Arguments

Response to Arguments Traversing the Rejection of claims 9-10 and 16 under 35 U.S.C. 103(a).

Appellants Specific Arguments Restated

I. Appellant urges the Office has not identified a particular motivation to make the specific invention. Appellant urges that a prima facie case of obviousness has not been established. Applicant urges that Samaritani teaches the use of a non-reducing sugar generally and sucrose specifically to enhance stability of the protein hCG (human Chorionic Gonadotropin) and liquid formulations thereof to maintain the hormonal activity of hCG. Appellant urges that Samaritani does not provide any teachings or suggestions regarding the use of non-reducing sugar for the stabilization of any other macromolecule. Appellant urges that Samaritani does not contemplate using a non-reducing sugar to maintain the immunogenicity of an antigen or a polysaccharide conjugated to a carrier protein.

Appellant urges that Sola-Penna et al. provides a study of trehalose as a stabilizer of "macromolecules" but the only macromolecules considered are enzymes and the stabilization studied was with respect to thermal effects on enzymatic activity. Sola-Penna et al. like Samaritani is not concerned with immunogenicity. Appellant urges that there is no teachings or suggestion in Sola-Penna et al. that trehalose would stabilize immunogenicity of an antigen.

Appellant urges that Anderson et al. provides no teachings regarding stabilization of the disclosed polysaccharide-protein carrier conjugates.

Appellant urges that none of the cited art alone or in combination teach or suggest the particular combination of trehalose with a polysaccharide-protein conjugate antigen.

Appellant urges that none of the cited art references alone or in combination teach or suggest that trehalose can decrease the decay of immunogenicity of polysaccharide-protein conjugate in a liquid vaccine composition.

II. Appellant urges that the combination of cited art references do not disclose or suggest all claim limitations. Appellant urges that Samaritani et al do not provide any teaching regarding the use of non-reducing sugar for stabilization of any other macromolecule besides hCG. Appellant urges that Sola-Penna et al like Samaritani et al is not concerned with or does not consider the immunogenicity of hCG. Appellant urges that there is no teaching in Sola-Penna et al that trehalose would stabilize immunogenicity of an antigen. Appellant urges that Anderson et al provides no teachings regarding stabilization of the disclosed polysaccharide-protein carrier conjugates.

III. Appellant urges that there is no reasonable expectation of success because the prior art teaches away from the claimed invention.

Examiner's Response to Appellant's Arguments

Applicant's arguments filed August 1, 2006 have been fully considered but they are not persuasive.

I. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Appellant must remember it is the combination of the prior art references that teach the claimed invention.

In this case, the combination of references teach the claimed invention for the following reasons:

Samaritani et al teach a method of using non-reducing sugars to maintain pharmaceutical compositions such as human Chorionic Gonadotropin (hCG) in the liquid state. Samaritani et al teach that it is known that purified proteins easily undergo degradation even due to the contact with atmospheric agents, which is also true for enzymes. Samaritani et al teach that proteins are easily stabilized by the addition of non-reducing sugars to the compositions. Samaritani et al teach that these compositions maintain a longer cycle life even if stored at room temperature (page 1).

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While it is true that Samaritani et al do not specifically teach the non-reducing sugar trehalose, Sola-Penna et al teach that trehalose is more effective at stabilizing macromolecules (e.g. protein, polysaccharides or enzymes) than other non-reducing sugars such as sucrose, maltose, glucose or fructose because trehalose occupies at least 2.5 more volume than sucrose, maltose, glucose or fructose.

Samaritani and Sola-Penna et al do not teach vaccine compositions comprising an antigen consisting of a polysaccharide bound to a carrier protein.

Anderson et al teach immunogenic conjugates comprising bacterial capsular polymer of a bacterial pathogen (antigen) and a protein carrier such as bacterial toxin or toxoid.

One of ordinary skill in the art would be motivated to combine the prior art references as presented above because the prior art teaches that the addition of non-reducing sugars to pharmaceutical compositions will aid to maintain the pharmaceutical composition in a liquid state. The prior art also teaches that trehalose is the most effective non-reducing sugar in stabilizing pharmaceutical compositions and protecting them from thermal inactivation. Therefore, one of ordinary skill in the art could reasonably conclude that the non-reducing sugar, trehalose, would be effective in maintaining immunogenic conjugates comprising bacterial antigen and protein carriers in a liquid state since sucrose has been disclosed in both Samaritani and Sola-Penna as a non-reducing sugar and Sola-Penna et al teach that trehalose, a non-reducing sugar is more effective than other non-reducing sugars such as sucrose, maltose,

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fructose or glucose. Thus, one of ordinary skill in the art would be motivated to use trehalose instead of other non-reducing sugars in pharmaceutical compositions.

To address Appellant's assertion that none of the cited prior art references recognize that trehalose can decrease the decay of immunogenicity of a polysaccharide-protein conjugate in a liquid vaccine composition, it should be noted that the combination of prior art references teach that trehalose is effective in protecting enzymes (antigens) from thermal inactivation. Sola-Penna et al, in particular disclose this property of trehalose. Thus, the combination of prior art references teach that trehalose can "preserve the immunogenicity" or decrease the decay of immunogenicity of pharmaceutical compositions.

II. To address Appellant's Arguments regarding the fact that that the combination of references do not teach or disclose all claim limitations, it is the Examiner's position that the combination of art references teach the claimed invention. As outline above, Samaritani et al teach that non-reducing sugars can be used to stabilize and maintain pharmaceutical compositions in liquid form even if they are stored at room temperature. Sola-Penna et al teach trehalose, which is the non-reducing sugar used in the claimed method. Sola-Penna also provide the motivation as to why the artisan of ordinary skill would use trehalose over other non-reducing sugars. As stated above, Sola-Penna et al teach that trehalose is more effective at stabilizing macromolecules than other non-reducing sugars because trehalose occupies at least 2.5 more volume than sucrose, maltose, glucose or fructose and this property of trehalose protect enzymes (e.g.

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proteins/antigen) against thermal inactivation. Anderson provides the polysaccharide antigen carrier conjugates to be maintained in the liquid state.

III. To address the Appellant's argument regarding the combination of prior art references not providing a reasonable expectation of success, it should be noted as stated above, Samaritani et al as well as Sola-Penna et al have demonstrated that non-reducing sugars can be used to stabilize pharmaceutical compositions and can maintain these compositions in liquid form.

To address Appellant's argument regarding the prior art references teaching away from the claimed invention, it should be noted that both Samaritani and Sola-Penna et al teach non-reducing sugars to stabilize pharmaceutical compositions. However, Sola-Penna et al teach that trehalose, a non-reducing sugar is more effective than other non-reducing sugars such as sucrose, maltose, fructose or glucose. Thus, one of ordinary skill in the art would be motivated to use trehalose instead of other non-reducing sugars in pharmaceutical compositions. The combination of art references have demonstrated that pharmaceutical compositions comprising polysaccharide-carrier protein conjugates can be stabilized and maintained in the liquid form, thereby preserving the immunogenicity of the conjugate. Thus, the combination of prior art references do not teach away from the claimed invention.

There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

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(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

Examiner's Answer Conclusion

For the above reasons, it is believed Examiner should be affirmed.

Respectfully submitted,



Vanessa L. Ford
August 1, 2007



Mark Navarro
Conferee

(ACTING SPE 1645)

MARK NAVARRO
PRIMARY EXAMINER



Nita Minnifield
Conferee

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